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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,754	12/13/2005	Takayuki Doi	2005_1863A	5099

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EXAMINER	
HUYNH, CARLIC K	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
09/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,754	DOI ET AL.	
	Examiner	Art Unit	
	Carlic K. Huynh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *8-14,16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,15 and 18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *13 December 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-21 are pending in the application, with claims 8-14 and 16-17 having been withdrawn, in response to the restriction requirement submitted on June 20, 2007. Accordingly, claims 1-7, 15, and 18-21 are being examined on the merits herein.

Election/Restrictions

2. Applicant's election of the claims of Group I, namely claims 1-7, 15, and 18-21, in the reply filed on July 12, 2007 is acknowledged. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 8-14 and 16-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made with traverse in the reply filed on July 12, 2007.

3. Applicants' election of: (1) Compound A, 8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrole[3,2,1-ij]quinoline-4-one, as the species of a compound having acetylcholine esterase inhibitory activity, in the reply filed on July 12, 2007 is acknowledged. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Accordingly, claims 1-7, 15, and 18-21 are examined on the merits herein.

The election/restriction requirement is deemed proper and is made FINAL.

Claims 1-7, 15, and 18-21 are directed at a preventive or remedy. In order to facilitate prosecution, these claims will be treated as pharmaceutical compositions and as such intended use is not given any patentable weight.

Information Disclosure Statement

The Information Disclosure Statement submitted on December 13, 2005, is acknowledged.

Specification

4. The use of the trademark Eudragit, HIGHBISWAKO, LOVELY WAX, ABISEL, EXISPROTAB, and AEROSIL has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7, 15, and 18-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for remedy, does not reasonably provide enablement for preventive. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:
(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). ***Nature of the Invention***:

The rejected claim(s) is/are drawn to a preventive or remedy urinary disturbance, dry mouth or overacitve bladder comprising a compound having acetylcholine esterase inhibitory activity and being sustantially free from butyrylcholine esterase inhibitory activity.

(2). ***State of the Prior Art***:

The skilled artisan would view that a compound that is a preventive of urinary

disturbance is highly unlikely.

(3). ***Relative Skill of Those in the Art***:

The relative skill of those in the art of urinary disturbance is extremely high.

(4). ***Predictability of the Art***:

The compound that is a preventive of urinary disturbance is highly unpredictable. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and that physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Thus, the state of the art is highly unpredictable.

(5). ***Breadth of the Claims***:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a a preventive or remedy urinary disturbance, dry mouth or overacitve bladder comprising a compound having acetylcholine esterase inhibitory activity and being sustantially free from butyrylcholine esterase inhibitory activity.

(6). ***Direction or Guidance Presented***:

The guidance given by the specification as to [8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one] as a preventive

for urinary incontinence is limited.

The disclosure of [8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one] as a remedy for urinary incontinence is adequate (Examples 1-6, pages 325-342).

(7). ***Working Examples***:

The working examples in the specification show [8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one] increased the amount of urination and maxium urine flow rate and enhanced the urination function of the bladder (page 334, lines 3-6). Thus, the working examples show [8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one] as a remedy, not as a preventive for urinary incontinence.

Note that lack of a working example to prevent, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

(8). ***Quantity of Experimentation Necessary***:

The specification fails to provide sufficient support of a preventive agent for an ocular disorder. As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of any drugs having the function recited in the instant claim suitable to practice the claimed invention.

Therefore, in view of the Wands factors, e.g. the predictability of the art, the amount of direction or guidence, and the lack of working examples discussed above, a person of skill in the art would not be able to fully practice the instant invention without ***undue experimentation***.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-7, 15, and 18-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear whether or not a "preventive or remedy" is a pharamceutical composition in instant claims 1-7, 15, and 18-21 and thus is considered indefinite.

Claim Rejections - 35 USC § 102

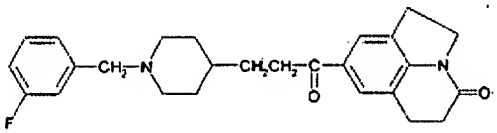
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-2, 6-7, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Ishihara et al. (JP2001-335576) as evidenced by Nagabukuro et al. (European Journal of Pharmacology, 2004, Vol. 494, pp. 225-232).

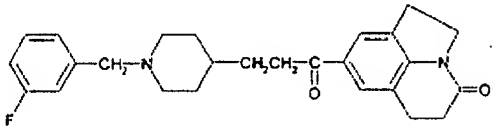
It is noted the machine translation of JP2001-335576 will be used for citation purposes.

Ishihara et al. teach a method of treating dysuria comprising administering [8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one], which has a chemical formula of,



(abstract and chemical formula 139). The compound has acetylcholine esterase inhibitory action ([0001]).

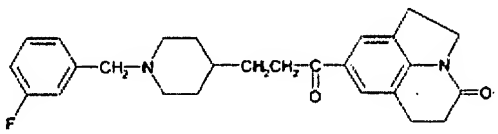
As evidenced by Nagabukuro et al., the compound of the formula,



is also known as TAK-802 and selectively inhibits acetylcholinesterase activity, which is unlike traditional carbamate acetylcholinesterase inhibitors that inhibit both acetylcholinesterase and butyrylcholinesterse activity (page 230). Thus TAK-802 is "substantially free from" butyrylcholine esterase activity.

Applicants' attention is directed to *Ex parte Novitski*, 26 USPQ2d 1389 (BOPA 1993) illustrating anticipation resulting from inherent use, absent a *haec verba* recitation for such utility. In the instant application, as in *Ex parte Novitski*, supra, the claims are directed to preventing a malady or disease with old and well known compounds or compositions. It is now well settled law that administering compounds inherently possessing a protective utility anticipates claims directed to such protective use. Arguments that such protective use is not set forth *haec verba* are not probative. Prior use for the same utility clearly anticipates such utility,

absent limitations distancing the proffered claims from the inherent anticipated use. Attempts to distance claims from anticipated utilities with specification limitations will not be successful. At page 1391, *Ex parte Novitski*, supra, the Board said "We are mindful that, during the patent examination, pending claims must be interpreted as broadly as their terms reasonably allow". *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989). As often stated by the CCPA, "we will not read into claims in pending applications limitations from the specification". *In re Winkhaus*, 52 F.2d 637, 188 USPQ 219 (CCPA 1975)." Thus, the compound of the formula,



inherently possesses the same chemical properties of a selective inhibitor of acetylcholine esterase activity.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 102(b).

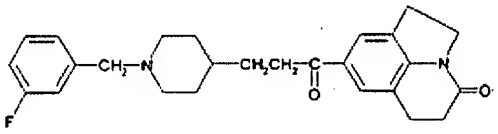
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 4-5, 18, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishihara et al. (JP2001-335576) as evidenced by Nagabukuro et al. (European Journal of Pharmacology, 2004, Vol. 494, pp. 225-232), as applied to claims 1-2, 6-7, and 15 above.

Regarding the ratio of 50% inhibitory concentration of butyrylcholine esterase to acetylcholine esterase as recited in claims 4-5, 18, and 20, the evidence of Nagabukuro et al. disclose the compound of the formula,



selectively inhibits acetylcholinesterase activity, which is unlike traditional carbamate acetylcholinesterase inhibitors that inhibit both acetylcholinesterase and butyrylcholinesterse activity (page 230). Thus the butyrylcholine esterase 50% inhibitory concentration is much greater than the acetylcholine esterase 50% inhibitory concentration, which closely meets the ratio of 50% inhibitory concentration of butyrylcholine esterase to 50% inhibitory concentration of acetylcholine esterase in instant claims 4-5, 18, and 20. It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the ratio of 50% inhibitory concentration of butyrylcholine esterase to acetylcholine esterase in a composition, according to the guidance set forth in Nagabukuro et al., to provide a composition having desired ratio of 50% inhibitory concentration of butyrylcholine esterase to acetylcholine esterase. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

9. Claims 3, 19, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishihara et al. (JP2001-335576) as evidenced by Nagabukuro et al. (European Journal of Pharmacology, 2004, Vol. 494, pp. 225-232), as applied to claims 1-2, 6-7, and 15 above, in further view of Servadio et al. (Urology, 1975, Vol. 5, No. 6, pp. 747-750).

Ishihara et al. do not teach an additional anticholinergic agent.

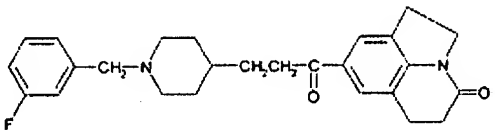
Servadio et al. teach a method for treating dysuria comprising administering nortriptyline chloride (abstract). Nortriptyline has anticholinergic properties (abstract).

Accordingly, absence the showing of unexpected results, it would have been obvious to a person of skill in the art at the time of the invention to employ the [8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one] composition of Ishihara et al. to be used with nortriptyline to treat dysuria because the compounds of Servadio et al. teach nortriptyline and according to Servadio et al., nortriptyline treats dysuria.

The motivation to combine the [8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one] compound of Ishihara et al. to the nortriptyline compound of Servadio et al. is that the nortriptyline compound of Servadio et al. can be used to treat dysuria.

It is noted that "It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose" and "It is obvious to combine two compositions taught by the prior art to be useful for the same purpose to form a third composition that is to be used for the very same purpose". *In re Kerkhoven*, 626 F.2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980).

Regarding the ratio of 50% inhibitory concentration of butyrylcholine esterase to acetylcholine esterase as recited in claims 19 and 21, the evidence of Nagabukuro et al. disclose the compound of the formula,



selectively inhibits acetylcholinesterase activity, which is unlike traditional carbamate acetylcholinesterase inhibitors that inhibit both acetylcholinesterase and butyrylcholinesterse activity (page 230). Thus the butyrylcholine esterase 50% inhibitory concentration is much greater than the acetylcholine esterase 50% inhibitory concentration, which closely meets the ratio of 50% inhibitory concentration of butyrylcholine esterase to 50% inhibitory concentration of acetylcholine esterase in instant claims 19 and 20. It is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the ratio of 50% inhibitory concentration of butyrylcholine esterase to acetylcholine esterase in a composition, according to the guidance set forth in Nagabukuro et al., to provide a composition having desired ratio of 50% inhibitory concentration of butyrylcholine esterase to acetylcholine esterase. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 223, 235 (CCPA 1955).

Double Patenting

Obviousness-Type

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

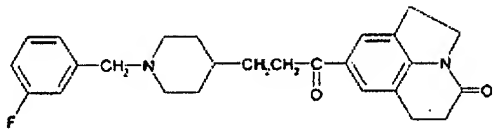
improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1 and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35 and 42-43 of copending Application Isihara et al. (11/475,881) in view of Ishihara et al (JP2001-335576).

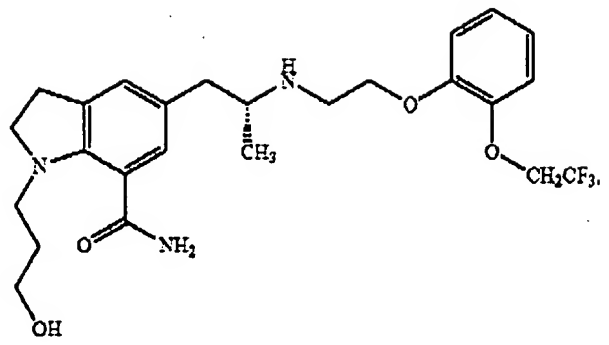
Ishihara et al. teach a method of treating dysuria comprising administering [8-[3-[1-[(3-fluorophenyl)methyl]-4-piperidinyl]-1-oxopropyl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-4-one], which has a chemical formula of,



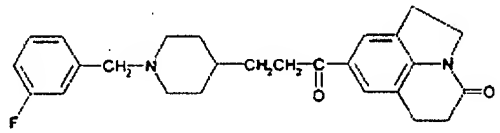
,

and an alpha-blocker (abstract and chemical formula 139).

It is obvious that dysuria of Ishihara et al. is the decreased state of excretory potency of the urinary bladder of Isihara et al. It is also obvious that the alpha-blocker of Ishihara et al. is prazosin, tamsulosin, or a compound of the formula,



of Isihara et al. It is further obvious that the non-carbamate amine compound having an acetylcholinesterase-inhibiting action of Isihara et al. is a compound of the formula,



of Ishihara et al.

Thus the claims of Isihara et al. (11/475,881) are not patentably distinct from the instant claims.

This is a provisional double patenting rejection since the conflicting claims have not been patented.

Conclusion

11. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carlic K. Huynh whose telephone number is 571-272-5574. The examiner can normally be reached on Monday to Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ckh

S. Wang

SHENGJUN WANG
PRIMARY EXAMINER